Increased Kidney Transplantation Utilizing Expanded Criteria Deceased Organ Donors with Results Comparable to Standard Criteria Donor Transplant

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Objective: To compare outcomes in recipients of expanded criteria donor (ECD) versus standard criteria donor (SCD) kidneys at a single center using a standardized approach with similar immunosuppression.

Summary Background Data: Expanded criteria deceased organ donors (ECD) are a source of kidneys that permit more patients to benefit from transplantation. ECD is defined as all deceased donors older than 60 years and donors older than 50 years with 2 of the following: hypertension, stroke as the cause of death, or preretrieval serum creatinine (SCr) greater than 1.5 mg/dl.

Methods: We retrospectively studied 90 recipients of adult deceased donor kidneys transplanted from October 1, 2001 to February 17, 2003, including 37 (41%) from ECDs and 53 (59%) from SCDs. ECD kidneys were used by matching estimated renal functional mass to recipient need, including the use of dual kidney transplants (n = 7). ECD kidney recipients were further selected on the basis of older age, HLA-matching, low allosensitization, and low body mass index. All patients received a similar immunosuppressive regimen. Minimum follow up was 9 months.

Results: There were significant differences in donor and recipient characteristics between ECD and SCD transplants. Patient (99%) and kidney graft survival (88%) rates and morbidity were similar between the 2 groups, with a mean follow-up of 16 months. Initial graft function and the mean 1-week and 1-, 3-, 6-, 12-, and 18-month SCr levels were similar among groups.

Conclusions: The use of ECD kidneys at our center effectively doubled our transplant volume within 1 year. A systematic approach to ECD kidneys based on nephron mass matching and nephron sparing measures may provide optimal utilization with short-term outcomes and renal function comparable to SCD kidneys.

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Due to changing donor demographics, excessive waiting times, and the increasing disparity between organ supply and demand, the use of kidneys from expanded criteria donors (ECDs) has become generally accepted and increasingly common.[1] In the last decade, the proportion of deceased donors older than 50 years of age has increased from 21% to 30%.[2,3] In addition, brain death resulting from cerebrovascular causes has increased from 26% to 41% among organ donors. However, median waiting times have doubled and the kidney waiting list has increased by 260%. During this same time period, the number of deceased donor kidney transplants has increased by only 16%.[1–3]

The burgeoning crisis in organ supply challenges the transplant community to maximize and optimize the use of organs from all consenting donors. The propriety of using kidneys from ECDs has been questioned because of concerns over diminished survival.[1,4–15] To promote the use of ECD kidneys, an analysis was performed of "expanded" donors by the Scientific Registry of Transplant Recipients (SRTR).[1,5,6] On the basis of this study, a consensus definition of an ECD kidney was developed according to basic donor characteristics that were associated with a relative risk (RR) of graft loss of >1.7 when compared with kidneys transplanted from standard criteria donors (SCD). For purposes of this SRTR study, SCD was defined as donors between 10 and 39 years of age who were without hypertension, who did not die of a cerebrovascular accident, and whose terminal predonation serum creatinine (SCr) level was <1.5 mg/dl.[6] On the basis of this analysis, the United Network for Organ Sharing (UNOS) introduced a new policy in the last quarter of 2001 that addressed special allocation issues pertaining to ECDs.[16] The purpose of this study is to report our initial experience with ECD versus SCD kidney transplants coincident with implementation of the UNOS policy, with special emphasis on nephron mass matching and nephroprotective measures to optimize kidney utilization.

MATERIALS AND METHODS

Study Design

Patients who received a deceased donor kidney transplant at Wake Forest University Baptist Medical Center between October 1, 2001 and February 17, 2003 were reviewed retrospectively. Specific exclusions during the study period included pediatric recipients (younger than age 18 years, n = 6), simultaneous kidney-pancreas transplant recipients (n = 15), and living donor kidney recipients (n = 33). A total of 90 patients met the study criteria and were categorized as ECD or SCD kidney transplants. Data were compiled from both prospective and retrospective databases, with confirmation by medical record review.

Definition

The UNOS definition of an ECD kidney is based on an SRTR analysis of primary deceased donor kidney transplants performed between March 6, 1995 and November 30, 2000.[1,5,6] A number of donor and recipient variables were included in the analysis, and a Cox proportional hazards model was used to determine the RR of graft failure. On the basis of this analysis of the data, RR of 1.7 (70% greater likelihood of graft loss) was chosen as the threshold for defining ECD. During the study period, 14.8% of transplanted kidneys had a RR of graft loss of >1.7, and 39% of procured kidneys from donors with a calculated RR > 1.7 were discarded. ECD was defined as all donors older than 60 years and donors older than 50 years with any 2 of the following criteria: (a) hypertension; (b) cerebrovascular cause of brain death; or (c) donor SCr > 1.5 mg/dl. For purposes of our study, any deceased donor not meeting the above criteria was defined as a SCD.

Donor Evaluation and Organ Management

No specific donor upper age limit was excluded from consideration, although the oldest donor in this series was 74 years old. In general, ECDs with other risk factors (positive hepatitis B or C serology, high-risk social/sexual behavior, central nervous system malignancy) were excluded from consideration. A history of diabetes was not a contraindication to using an ECD kidney, unless the donor had documented proteinuria or a decline in renal function.

The Cockcroft-Gault formula was employed to estimate donor creatinine clearance, using both actual and ideal body weight to calculate a range of potential donor kidney function and to determine single- or dual-kidney transplantation (DKT) into a single recipient.[17,18] If the estimated creatinine clearance was > 70 mL/min, then a single-kidney transplant was performed, preferably into a recipient with a body mass index (BMI) < 25 kg/m^2.[19,20] If the estimated creatinine clearance was < 50 mL/min, then the kidney(s) were not used. If the estimated creatinine clearance was between 50 and 70 mL/min, then a DKT was performed using a midline

intraperitoneal approach.[13,14,18–22] In general, if the terminal SCr was > 2.0 mg/dl, then the kidney(s) were not used.

Donor kidney biopsy was also used to assist in the evaluation of preexisting and terminal renal parenchymal injury.[19,23–27] In general, if the biopsy showed moderate to severe vascular changes (atherosclerosis, intimal thickening or hyalinization, or microvascular thrombosis), moderate to severe tubular changes (necrosis, edema, or atrophy), or moderate to severe interstitial changes (infiltrates or fibrosis), then the kidney was not accepted for transplantation. In addition, > 50% glomerulosclerosis was an absolute contraindication, and 35 to 50% glomerulosclerosis a relative contraindication for kidney utilization.[23–27]

Whenever possible, ECD kidneys were placed on a pulsatile perfusion pump to minimize preservation injury, maintain functional reserve, and provide another means of assessment.[28–31] Within our organ procurement organization, kidneys are placed routinely on the perfusion pump at the accepting center's discretion or if the donor is older than 40 years, is hemodynamically unstable, is oliguric (urine output, <100 mL/h), has a SCr > 1.2 mg/dl, or has a history of hypertension or diabetes. Although pump parameters were not exclusively used to discard kidneys, a flow rate greater than 80 mL/min and a resistance below 0.35 mm Hg after a minimum of 6 hours on the perfusion apparatus were considered as thresholds for utilization.[32]

Recipient Evaluation and Selection

At our center, no specific upper age limit is an absolute contraindication to kidney transplantation, although the oldest recipient in this series was 76 years old at the time of transplant. All patients undergo a comprehensive pretransplant medical, psychosocial, and financial evaluation, with emphasis placed on the cardiovascular system to determine operative risk and physiologic age. Patients are discussed at a multidisciplinary pretransplant selection committee meeting, with candidacy for transplantation determined by a group decision. At this time, patients are assigned a risk assessment (to aid in waiting list maintenance and follow-up), and a decision is made whether or not to list the patient as willing to accept an ECD donor. In general, if the patient is younger than 30 years of age, highly sensitized (panel reactive antibody [PRA] titer > 50%), extremely obese (BMI > 35 kg/m^2), or a retransplant candidate, then the patient is not listed for an ECD donor. In addition, the patient or referring physician may elect to decline the option of an ECD, particularly if the patient is not yet on dialysis, is doing well on dialysis, or has a potential living donor. If the patient is either hepatitis B or C–positive, we may elect to leave them off the ECD list because our experience has shown that these patients may be transplanted relatively quickly with a SCD kidney.[33]

At the time of transplantation, patients were selected on the basis of ABO blood type match, waiting time, human leukocyte antigen (HLA)-matching, a negative lymphocytotoxic crossmatch, and special listing for ECD in accordance with UNOS guidelines. Whenever possible, ECD kidneys were used by matching estimated renal functional mass to recipient need, including the use of DKTs (n = 7). ECD kidneys are defined by suboptimal nephron mass; therefore, recipient selection was based on older age (usually > 40 years), low BMI (usually < 25 kg/m^2), and low immunologic risk (primary transplant, HLA-matching, and low PRA titer, usually 0%). For DKT, recipient selection was reserved for patients < 60 years of age because of the greater anesthetic and surgical risks associated with this procedure.[13,14,18–22] In addition, specific informed consent was obtained for performing a kidney transplant from an ECD either as a single or DKT.

Perioperative Management and Immunosuppression

Perioperative antibiotic prophylaxis consisted of a single preoperative dose, an intraoperative dose 3 hours after the initial dose, and 3 postoperative doses over 24 hours of cefazolin (1 g given intravenously). All patients received a single-strength sulfamethoxazole/trimethoprim 1 tablet 3 times weekly for 12 months for prophylaxis against *Pneumocystis carinii* pneumonia. Antifungal prophylaxis consisted of oral fluconazole 200 mg/d for 1 to 2 months. Antiviral prophylaxis included oral valganciclovir 450 mg/d for 3 months (with dosage adjustments for renal dysfunction and leukopenia) when either the donor or recipient was cytomegalovirus (CMV)–seropositive.[34] If both the donor and recipient were CMV-seronegative, then 400 to 800 mg of oral acyclovir twice daily was administered for 3 months. If the donor was CMV-seropositive and the recipient CMV-seronegative (primary CMV exposure), then 900 mg/d oral valganciclovir (with dosage adjustments as above) was given for 6 months.

All deceased donor kidney transplant recipients received antibody induction with rabbit antithymocyte globulin (rATG, Thymoglobulin; Sangstat Medical Corporation, Fremont, CA) at a dose of 1.5 mg/kg (maximum dose, 150 mg) based on actual body weight.[35] Administration was through a central line using a 0.22-μm filter as a continuous infusion over 6 hours for the first dose, which was started intraoperatively. Premedication of the first dose consisted of bolus methylprednisolone (500 to 1000 mg intravenously). Subsequent rATG infusions were administered over 4 hours as tolerated at alternate day intervals (postoperative day 2, 4, and so on) for a minimum of 3 doses and a maximum of 7 doses. Premedication for subsequent doses included 650 mg of oral acetaminophen and 25 to 50 mg of oral diphenhydramine.

Only 3 doses of rATG were given if the patient experienced immediate graft function. If the patient experienced slow (SCr > 3.0 mg/dl on postoperative day 5) or delayed graft function (DGF; defined as the need for dialysis in the first week posttransplantation), then rATG was continued at alternate day intervals until the SCr was < 3.0 mg/dl, the patient had a therapeutic tacrolimus (TAC) level, or a total of 7 doses had been administered.[35] If the patient did not have adequate renal allograft function by postoperative day 10, then a kidney biopsy was performed. The rATG dose was adjusted if the total white blood cell count was < 3000/mm^3 or if the platelet count was < 80,000/mm^3.

Maintenance immunosuppression consisted of TAC, mycophenolate mofetil (MMF), and tapering doses of corticosteroids.[36] TAC was started at 1 to 2 mg orally twice daily only after the patient had exhibited a brisk diuresis and a declining SCr (< 4.0 mg/dl). For ECD kidney recipients, the target 12-hour TAC trough level was 6 to 10 ng/ml for the first 3 months after transplant and 4 to 8 ng/ml thereafter in the absence of rejection or specific drug toxicity. For SCD kidney recipients, the target TAC level was 8 to 12 ng/ml for the first 3 months and 6 to 10 ng/ml thereafter.

Oral MMF was begun immediately postoperatively at 500 mg twice daily and increased to 1 g twice daily after completion of rATG antibody induction therapy.[36] However, for patients older than 60 years of age, the MMF dose was continued at 500 mg twice daily long-term. The MMF dose was reduced (or the dosing schedule adjusted) in patients with gastrointestinal intolerance (nausea, vomiting, or diarrhea) or when the total white blood cell count was < 3000/mm^3. MMF was discontinued temporarily in patients with active infection or septicemia or when the total white blood cell count was < 2000/mm^3; it was restarted later at a reduced dosage. After the first 3 months, the usual MMF dose was 500 to 750 mg twice daily in the absence of rejection.

Corticosteroids were administered as 500 to 1000 mg of intravenous methylprednisolone during surgery, followed by 250 mg on postoperative day 1, which was then tapered to 20 mg/d oral prednisone at 1 week. A gradual steroid taper was then used, aiming at an oral prednisone dose of 15 mg/d at 2 weeks, 10 mg/d at 1 month, and 5 mg/d at 2 months after transplant in the absence of rejection.

Posttransplant Management

Antiplatelet therapy consisting of oral aspirin (81 mg/d) was administered to all patients. Treatment of hypertension, hyperlipidemia, anemia, diabetes, and other medical conditions was initiated as indicated aiming to maintain the blood pressure < 140/90 mm Hg, fasting serum cholesterol < 200 mg/dl, hematocrit > 30%, and fasting blood sugar < 126 mg/dl. After hospital discharge, patients were followed in the Transplant Clinic twice weekly for 1 month, then once weekly for 1 month, and then every 2 weeks for 1 month before being referred back to their nephrologist for long-term care. Patients were next scheduled to be seen in the Trans-

plant Clinic at 1 year after transplant and annually thereafter. If clinically indicated, however, patients returned to the Transplant Clinic on an as needed basis.

The diagnosis of renal allograft rejection was suggested by an unexplained increase in SCr of >0.3 mg/dl or a 25% increase from baseline level and confirmed by ultrasound-guided percutaneous biopsy. All biopsy-proven rejection episodes were treated on the basis of severity. Mild rejection episodes were treated with 500 to 1000 mg/d intravenous methylprednisolone for 3 to 5 doses and/or an oral prednisone recycle. Mild rejection episodes without biochemical evidence of improvement or unresolved on a repeat biopsy within 2 to 3 weeks (persistent or steroid-resistant rejection) were treated with rATG therapy. Moderate and severe rejection episodes were also treated with rATG for 5 to 10 doses depending on biochemical and clinical response.

CMV infection was defined as a positive blood culture (early antigen) or polymerase chain reaction (PCR) assay, and CMV disease was defined as symptomatic CMV infection or histologic evidence of tissue invasion.[34,37] Treatment of CMV infection consisted of intravenous ganciclovir or oral valganciclovir for 2 to 4 weeks and selective use of CMV hyperimmune globulin (CytoGam; MedImmune Inc., Gaithersburg, MD) concomitant with a reduction in immunosuppression. Polyomavirus-induced nephropathy was diagnosed on the basis of renal allograft biopsy and treated with a reduction in immunosuppression, conversion from TAC to sirolimus, and low-dose intravenous cidofovir.[38] Urine cytology for decoy cells, blood PCR for polyomavirus, and kidney transplant biopsies were not performed unless clinically indicated in this series.

Statistical Analyses

Data are reported as mean ± SD and ranges. Renal allograft loss was defined as death with function, transplant nephrectomy, return to dialysis, or return to the pretransplant SCr level. Univariate analysis was performed by the unpaired t test for continuous variables, the χ^2 test for categorical variables, and Fisher exact test when data were sparse.

RESULTS

Over a 17-month period, 90 deceased donor kidney transplants were performed at our center, including 37 (41%) from ECDs and 53 (59%) from SCDs. Most of the ECD kidneys had been refused by one or more transplant centers before acceptance by our center, and many were targeted for discard. Among the 37 ECDs, a total of 7 DKTs were performed. Donor, recipient, and transplant characteristics are depicted in Tables 1 and 2. There were significant differences in donor and recipient characteristics between ECD and SCD transplants. The ECDs were characterized by older donor age (mean years, 63 ECD versus 31 SCD), a higher donor BMI (mean kg/m², 30 ECD versus 23 SCD), a higher

TABLE 1. Donor Characteristics*

	ECD (n = 37)	SCD (n = 53)	*P*-value
Age (yr)	63 ± 6.5	31 ± 14	<0.001
BMI (kg/m²)	30 ± 10.5	23 ± 4.9	<0.001
Cause of death: cerebrovascular	33 (89%)	15 (28%)	<0.001
History of hypertension	22 (59%)	10 (19%)	<0.001
Machine preservation	28 (76%)	10 (19%)	<0.001
Serum creatinine (mg/dL)	1.0 ± 0.4	1.1 ± 0.5	NS
Estimated creatinine clearance (mL/min)	67 ± 24	94 ± 38	<0.001
Cold ischemia time (hr)	21.9 ± 8.8	20.2 ± 6.0	NS

*Mean ± SD.

rate of cerebrovascular brain death (89% ECD versus 28% SCD), a higher incidence of preexisting donor hypertension (59% ECD versus 19% SCD), and a higher rate of machine preservation (76% ECD versus 19% SCD; all $P < 0.001$; Table 1). Mean donor SCr levels and cold ischemia times were similar in both groups, but the calculated donor creatinine clearance was lower in the ECD group (mean ml/min, 67 ECD versus 94 SCD; $P < 0.001$; Fig. 1).

There were significant differences (all $P < 0.05$) in recipient age (mean years, 55 ECD versus 48 SCD), 0-antigen mismatches (11% ECD versus 42% SCD), HLA-matching (mean, 2.1 ECD versus 3.1 SCD), and low allosensitization (86% ECD versus 62% SCD, Table 2). Other recipient characteristics (gender, ethnicity, BMI, diabetes, and waiting time) were similar between groups, although the proportion

TABLE 2. Recipient and Transplant Characteristics*

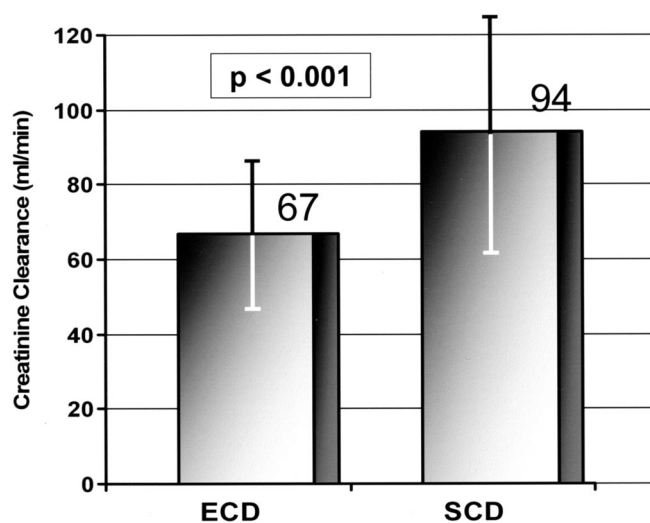|	ECD (n = 37)	SCD (n = 53)	*P*-value
Age (yr)	55 ± 11	48 ± 12	0.003
Age > 60 yr	15 (41%)	8 (15%)	<0.001
BMI (kg/m²)	24.0 ± 4.5	25.4 ± 5.3	NS
Gender (male)	24 (65%)	28 (53%)	NS
History of diabetes	10 (27%)	18 (34%)	NS
African-American	15 (40%)	18 (34%)	NS
Retransplant	2 (5%)	11 (21%)	0.065
HLA-match (A,B,Dr)	2.1 ± 1.8	3.1 ± 1.4	<0.001
0-Antigen mismatch	4 (11%)	22 (42%)	0.002
0% PRA	32 (86%)	33 (62%)	0.016
PRA > 40%	1 (3%)	14 (26%)	0.003
Waiting time (mon)	26 ± 19	31 ± 28	NS

*Mean ± SD.

FIGURE 1. Calculated creatinine clearance, using ideal body weight, in ECDs versus SCDs.

of retransplants trended higher in the SCD group (5% ECD versus 21% SCD; $P = 0.065$).

Patient (99%) and kidney graft survival (88%) rates were similar between groups with a mean follow-up of 16 months (Table 3). The incidence of DGF trended lower in the ECD group (11% ECD versus 21% SCD; $P = 0.26$). The time to achieve a posttransplant SCr < 3.0 mg/dl was similar (mean, 8 days) between groups, as was length of initial hospital stay. The incidence of acute rejection (14% overall), major infection (32% overall), reoperations (24% overall), and readmissions (56% overall) were similar between groups. Initial hospital charges (mean, $65,544 overall) were similar.

However, the incidence of CMV infection and polyomavirus-induced nephropathy were higher in the ECD group ($P = 0.004$ and $P = 0.066$, respectively; Table 3).

There was a total of 11 (12.2%) grafts lost in the study, including 5 in the ECD group and 6 in the SCD group. The causes of graft loss in the ECD group included acute rejection due to noncompliance (2 cases) at 3 and 15 months, polyomavirus-induced nephropathy (2 cases) at 5 and 7 months, and poor graft function/drug toxicity at 6 months posttransplant. In the SCD group, the causes of graft loss were thrombotic microangiopathy/antibody-mediated rejection (in 2 retransplant cases) at 2 weeks and 3 months, allograft thrombosis (pediatric donor kidney) at one day, acute rejection due to noncompliance at 5 months, death with a functioning graft due to a motor vehicle accident at 10 months, and chronic allograft nephropathy at 13 months posttransplant. The mean 1-week and 1-, 3-, 6-, 12-, and 18-month SCr levels were similar between groups (Fig. 2). The use of ECD kidneys effectively doubled the kidney transplant volume at our center within 1 year (Fig. 3).

DISCUSSION

According to recent statistics, there are nearly 300,000 patients on dialysis in the United States, and the overall incidence and prevalence of end-stage renal disease (ESRD) continue to increase at 1% and 2.4% per year, respectively.[39] In addition, the median age of the entire incident and prevalent populations likewise continues to increase and is currently 65 and 58 years, respectively. At present, there are over 59,000 registrations on the UNOS waiting list for kidney transplantation, and it is not unrealistic to presume that many other patients currently on dialysis could benefit from kidney

TABLE 3. Results*

|	ECD (n = 37)	SCD (n = 53)	*P*-value
Patient survival	37 (100%)	52 (98%)	NS
Graft survival	32 (86.5%)	47 (89%)	NS
Delayed graft function	4 (11%)	11 (21%)	0.26
Follow-up (mon)	15.4 (Range 9–24)	17.5 (Range 9–25)	NS
Days to SCr <3.0 mg/dL (days)	8.3 ± 10.7	8.2 ± 11.4	NS
Length of initial hospital stay (days)	8.9 ± 4.3	8.1 ± 4.0	NS
Initial hospital charges ($ US)	67,539 ± 13,608	64,169 ± 18,802	NS
Readmissions	20 (54%)	30 (57%)	NS
Re-operations	6 (16%)	16 (30%)	NS
Acute rejection	5 (13.5%)	8 (15%)	NS
Major infection	13 (35%)	16 (30%)	NS
CMV infection	5 (16%)	0	0.004
Polyomavirus-induced nephropathy	3 (8%)	0	0.066

*Mean ± SD.
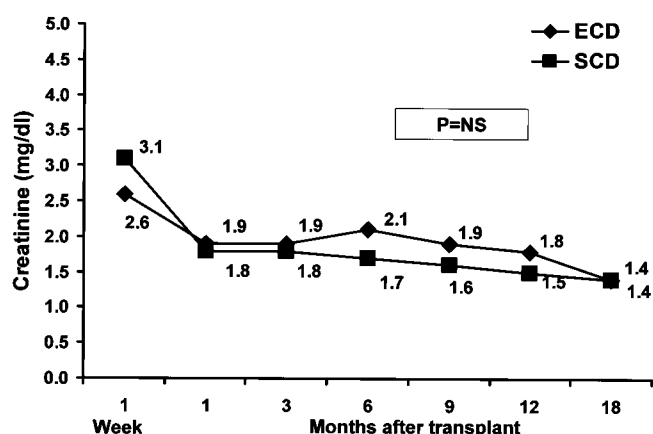
FIGURE 2. Mean serum creatinine levels at selected time points in ECD versus SCD kidney recipients.

transplantation. In the last decade, median waiting times have doubled from 600+ days to 1200+ days, and the kidney waiting list has increased by 260%.[1–3] The waiting list has become a "waiting to die" list, as 5% of patients on the kidney waiting list die each year. From 2000 to 2001, the kidney waiting list increased proportionally by 7.6%, whereas deceased kidney donors increased by only 1.4%.[1–3] In 2002, for the first time, the number of living donor kidney transplants performed in the United States actually surpassed the number of kidney transplants from deceased donors. According to Ojo et al, "in the face of a critical shortage, it is unrealistic to hope for pristine organs for all patients."[4]

Since 1992, there has been a progressive increase in the median age of deceased donors, and cerebrovascular events have now become the leading cause of brain death, resulting in deceased organ donation.[1–3] Despite public and professional education efforts, the number of deceased organ donors has become static in recent years. Transplantation has become the practice of rationing, with transplant centers functioning as gatekeepers rather than providers. Efforts to reduce waiting time include liberalizing criteria for living and deceased donors, performing DKTs, and using nonheartbeating donors. According to Becker et al, "Transplantation of marginal organs carries with it a great responsibility on the part of the transplant team. They must consider who will benefit the most from such organs and they must consider the toll that these organs might take."[40,41]

The decision to use an ECD kidney is complex because there are data to suggest that these kidneys have a higher rate of primary nonfunction, DGF, rejection, and a greater susceptibility to preservation injury, drug toxicity, and the effects of posttransplant hypertension.[1,4–15,40,42] In addition, ECD kidneys are believed to be more resource-intensive and costly.[7,9,43] Moreover, the longevity of an ECD kidney is believed to be much shorter, with the half-life estimated to be 4 to 6 years compared with 8 to 12 years with a SCD kidney from a deceased donor.[1,4–7] However, knowing that the half-life of any deceased donor kidney is much less than a living donor kidney has never been viewed as an impediment to using SCD kidneys. For these reasons, guidelines have been promulgated regarding the appropriate use of ECD kidneys to include recipients older than age 60 years, diabetic patients older than age 40 years, patients doing poorly on dialysis or with dialysis access failure, or patients with limited life expectancy.[1,44–46] These guidelines are based on the principle of improving access to transplantation for patients whose life expectancy is less than their predicted waiting time for a kidney.[47,48] For example, there are data to suggest that the wait for a deceased donor kidney has surpassed a diabetic patient's ability to survive on dialysis.[47–49] At present, however, the optimal use of ECD kidneys remains poorly defined because the available long-term data are limited. Moreover, the propriety of using ECD kidneys remains an ongoing issue, and it is uncertain whether ECDs are a bandwagon or a treadmill!

It is our contention that ECD kidneys are defined by suboptimal nephron mass, so it may be inappropriate to place an ECD kidney into a high medical (or immunologic) risk patient unless that recipient is matched according to nephron "need."[13,19,50,51] Consequently, whenever possible, we attempted to select the potential recipient on the basis of their estimated need for nephron mass, using such criteria as older age (> 40 years), low BMI (< 25 mg/kg^2), low immunologic risk (primary transplant, 0% PRA, HLA-matching), and informed consent, rather than automatically relegating the ECD kidney to a "marginal" recipient.[52] Since many of these kidneys were refused by all other centers, we were often afforded the opportunity to select an appropriate recipient matched to the estimated nephron mass of the donor.
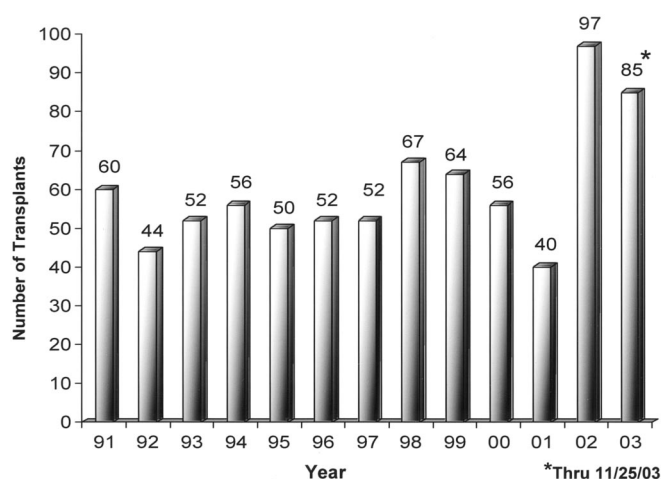

FIGURE 3. Volume of kidney transplant activity at our center since 1991.

In addition, our management protocol for the ECD kidney was based on a number of nephron-sparing maneuvers, including minimizing cold ischemia time, pulsatile perfusion preservation, front-loaded immunosuppression with rATG to minimize preservation injury and rejection, delayed administration of a calcineurin inhibitor, and targeting lower TAC levels long-term to minimize drug toxicity. Since many of these patients were selected on the basis of low immunologic risk, we felt comfortable with targeting lower TAC levels to achieve a balance between efficacy and toxicity.

In this study, the ECDs were twice as old and had significantly more comorbid conditions, resulting in an estimated renal function that was only 71% of the estimated renal function of the SCDs. Implementation of the UNOS policy had no discernible effect on minimizing preservation time, which was greater than 20 hours for both groups. Inspite of these drawbacks, the use of pulsatile perfusion preservation in the majority of the ECD kidneys remarkably led to a DGF rate that was almost half of that seen in the SCD kidneys. Although the ECD kidney recipients were older, fewer than half were older than 60 years and only 27% were diabetic. African-Americans accounted for 40% of the ECD recipient pool. In the SCD group, 42% of the patients received 0-antigen mismatched kidneys, but more patients in this group were sensitized or received retransplants. Time on the waiting list was no different between groups and was not a major factor in recipient selection in the ECD group. None of our ECD recipients were selected on the basis of either medical urgency or dialysis access failure. Importantly, donor BMI in the ECD group was much higher than recipient BMI, whereas donor and recipient BMI were similar in the SCD group. In essence, a higher BMI in an older donor translates into a predicted creatinine clearance by the Cockcroft-Gault equation that is "matched" to an adult recipient with a lower BMI.

Therefore, by avoiding high BMI, young, and presensitized patients, we were able to achieve favorable short-term results with ECD kidneys that were comparable to concurrently transplanted SCD kidneys. A number of clinical outcomes and parameters of morbidity and resource utilization were similar between groups. We did not note either an increased susceptibility to preservation injury or an increased risk of rejection in the ECD group. In addition, initial and short-term renal function was comparable. Interestingly, the only adverse effect that was observed in our study was a greater propensity to viral infection (either CMV or polyomavirus) in the ECD patients, suggesting either over immunosuppression (in an older recipient population) or perhaps preexisting injury contributing to subsequent viral activation. Clearly, long-term follow-up is necessary to fully delineate the risks and benefits of using ECD kidneys in these patients.

On the basis of this preliminary experience, we do not believe it is necessary to match the life expectancy of the recipient with the kidney, nor do we believe that the use of ECD kidneys can be optimized only if they significantly decrease waiting time.[1,7] If one places a high-risk kidney into a high-risk recipient, then it is not unexpected that the clinical outcomes are inferior. Since donor and recipient risk factors for graft loss may be cumulative, it may be more appropriate to place an ECD kidney into a low-risk (and low functional need) recipient.[53] By incorporating nephron mass matching and nephron sparing measures into the allocation and management algorithm, we believe that one can achieve excellent short-term outcomes with ECD kidneys that rival those currently being attained with SCD kidneys. Ultimately, a number of important goals can be realized, including maximal and optimal utilization of ECD kidneys, minimizing kidney discard and waiting list deaths, improving rehabilitation and quality of life, controlling resource utilization, and respecting individual autonomy.

ACKNOWLEDGMENTS

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Discussions

DR. RICHARD J. HOWARD (Gainesville, Florida): Organ shortage is the problem facing transplantation today. In an attempt to avoid wastage of organs, a couple of years ago UNOS, which stands for United Network for Organ Sharing, which in this country is in charge of allocating all organs for transplantation, noted that kidneys from donors older than 50 were often wasted. So it decided that it would have a separate waiting list of patients who were willing to take kidneys from certain donors over 50 and all donors over 60, and all transplant centers had to have the patients sign an informed consent that they would be willing to accept these kidneys. And that was approved a couple of years ago by the UNOS Board.

It was presented to the UNOS Board—I was a member at that time—by the statisticians at UNOS having evaluated their very extensive database, that these kidneys had 1.7 times the relative risk of graft loss. I wasn't quite sure what that

meant. Afterwards, I went around individually during a break to every member of the Board and to virtually every member of the UNOS staff who was there and asked them if they understood it. Not a single person could explain it to me in a clear way. And those who could explain it disagreed with each other. What it means is that these kidneys have 1.7 times the risk of graft loss compared not to standard criteria kidneys but to kidneys that have a relative risk of 1. And those are kidneys from donors between 20 and 30 years old. And that is how the statistics work.

We should be grateful to the authors because they have shown us that these kidneys, in fact, which are still being turned down by many transplant centers, can have a graft survival comparable to those of standard criteria donors.

And yet we worry—at least I do—that kidneys from these donors still have a price to be paid by the recipients. Because kidneys age, unlike some organs like the liver which don't seem to age. And we pay a price for getting older. There are significant pathologic changes that occur in all of us just by the fact that we are still alive.

I would like to ask the authors—they seem to be very liberal in their criteria of pathologic changes and they are willing to transplant—now that there has been more time followed up since the submission of the abstract, have there been any changes noted in the survival for these 2 groups?

The second question I would like to ask is how they chose, as they outlined, which recipients these extended criteria donors went into. And yet according to UNOS, which determines who these organs are supposed to go into, when a kidney becomes available you get what you call a match run, and that lists all the patients in a certain order based on certain points that UNOS establishes, and you have to offer the kidney to those patients in that order or you violate UNOS protocol. And it differs from the set of criteria that the authors chose.

And I am not saying they are unreasonable, but I would like to know, did they violate the UNOS protocol for organ allocation? And that is not always an unreasonable thing to do. But since one of the authors was a former president of UNOS and was in charge of enforcing the UNOS allocation scheme, how did they get around that where they thought it was appropriate?

Finally, they didn't transplant these kidneys into obese patients who had a body mass index greater than 25. They were overweight, not obese. And yet the creatinine clearance really is more related to muscle mass than to body mass index because fat really doesn't contribute anything to creatinine or to renal function. So I would like to know why they chose that parameter.

DR. LOUIS G. BRITT (Memphis, Tennessee): This excellent study and presentation details a very carefully designed method to get more organs and get them into people. Dr. Rohr has shown that this can be done.

I object to many UNOS rules because that removes all judgment and personal knowledge of the patients. Dr. Rohr has done the right thing. He has put these organs into patients who are good risk recipients. If you put them into bad recipients, you almost guarantee they are going to fail.

Dr. Rohr, I have a couple of questions.

First, your machine preservation, which you did in 76% of your patients. I think that that may be the most significant factor in improving the long-term results, the function of these kidneys. Why did you do it in those 76% and not in 25%? And how did you decide whether to use machine preservation or not?

In your standard criteria patients only 19% had machine preservation and there was increased delayed graft function in that group. Why don't you just machine preserve all of them, both extended and standard criteria donors?

Cold ischemia time was 20 hours in both groups. I couldn't really determine whether you added cold ischemia time and preservation time together. Would you clarify that to me as to how much is machine preservation and how much is true cold ischemia time?

Another question was I am not sure exactly how you use your biopsy information. As you know, we biopsy everything multiple times. Did you use it in your pre-implantation decision and did you use it in your delayed graft function kidneys to determine immunosuppression?

One final question. I believe you used ATG in all your patients, both expanded and standard criteria, and I think that is important. Would you clarify that? Secondly, why didn't you look at rapamycin as a less nephrotoxic agent?

Finally, I think this experience suggests—or I hope it suggests—to you further avenues of investigation and exploration regarding one outstanding issue that I think has never been explored carefully: How do we make a better donor out of the current marginal donor?

DR. RALPH R. BOLLINGER (Durham, North Carolina): I rise to congratulate Dr. Rohr and his colleagues on bringing us an important message. It has changed a lot from the years when we only took the left kidney from a young, healthy donor. The reality now is we need these extended donor kidneys at a time when diabetes has replaced glomerulonephritis as the main cause of renal failure in our recipients. And it is about diabetes I want to inquire.

Dr. Rohr, does diabetes play any role in determining an extended donor? Is a juvenile diabetic who ends up brain dead or a long-standing insulin-dependent diabetic who ends up brain dead not also an extended donor? And in your recipients how do you regard diabetes? I would ask how the Winston-Salem group treats diabetes with extended donor kidneys.

Dr. Mark G. Deierhoi (Birmingham, Alabama): I think this is a very important paper, not just because it shows us that we can use extended criteria donor kidneys with excellent outcomes but because it answers to some extent one of the questions that we have about extended donors. And I think one of the reasons why these kidneys are discarded frequently is that we just don't know what the upper parameters are for an extended donor criteria for things like age, creatinine, and some of the other factors that were presented by Dr. Rohr and are listed in the manuscript. So I think that they have contributed significantly to our information on extended donors by giving their parameters for what are unacceptable criteria for someone to be an extended donor; for example, a creatine of 2 and their biopsy results and their data on calculated creatinine clearance.

I have 3 questions for the authors related to the paper. One, in your extended donors do you have a cut-off for overall ischemic time in terms of whether you will accept an organ or not; for example, if you were offered a kidney from California that was going to be preserved for 24 hours on ice before you received it? Would you accept an organ with that sort of cold ischemic time without pulsatile perfusion?

Secondly, I wonder if you have information on whether or not the introduction of your more aggressive approach to extended donors has had an impact on the discard rate of these kidneys within your own area?

Finally, because you have shown such good results with extended criteria donors, are you contemplating at all expanding your accepted limits for these donors?

Dr. Michael S. Rohr (Winston-Salem, North Carolina): I would like to thank the discussants for their insightful comments and questions.

Dr. Howard, at this point in the follow-up of these 2 groups of patients, there is no difference in the outcome. Certainly continued follow-up is very important.

We probably do not violate the UNOS protocol for placement of these kidneys. Certainly there is a feature in the UNOS allocation system to explain why a patient higher on the waiting list is not selected for transplant. We do not select overweight patients and we do not select older patients for double kidney transplants. We look over the list carefully, and it does require some time and effort when ECD kidneys are offered to us.

Why did we choose low body mass index recipients? That is a good question, since it is difficult to really know what the true creatinine clearance is based on the weight. We calculate the creatinine clearance based on ideal body weight and actual body weight, and there is certainly a discrepancy. We assess this data and make an appropriate judgment about the recipient. It is not an exact science, which we readily admit.

Dr. Britt asked about machine preservation. We did use it more commonly in the ECD patients. We use it with standard criteria donors when we have the opportunity. However, if we can do a fairly quick cross match and get to the operating room without delay, we feel it may not be worth the effort of putting them on the pump for a short period of time. The use of machine preservation is polarized between those of us who are wedded to it and those who do not consider it important. It is an important feature in management of organs in our program.

The biopsy information is used to exclude kidneys that we will not transplant. From a practical point of view, we did not use kidneys that had a sclerosis of more than 30% of glomeruli. If there is evidence of vascular disease, interstitial inflammation and infiltrate, or interstitial fibrosis, we do not use the kidneys. I recognize that there are not established criteria for this, and certainly provides an opportunity for study. We do use biopsy early after transplant if the creatinine is not falling to determine whether we are dealing with acute tubular necrosis or rejection.

We did use rabbit antithymocyte globulin in all patients in this study. We did not use rapamycin routinely. The best use of rapamycin is unclear to us. In our own hands, based on a series of patients in a randomized trial, there is an increased incidence in wound complications and lymphoceles.

How do we make better donors? We do that with early donor referral and aggressive management. Most of our donors realistically have an 18–24 period of time in which the organ procurement coordinators can manage them. We commonly see creatinine levels fall considerably. We use kidneys with a peak creatinine of 4 if it drops to near pre-death creatinine with good donor management. I do think donor management plays a role and recognize that like other things in transplantation it is not an exact science. It is also an area that could be studied.

Dr. Bollinger asked a question about the role diabetes plays in the selection of kidneys for transplantation. We do use donors who have diabetes. We exclude them if they have proteinuria or if there are biopsy findings as described above. How do we treat diabetes in the recipient? We monitor glucose and give insulin. We do not have any special insight into diabetic management after transplant. Obviously the best treatment of diabetes is successful pancreas transplantation.

Dr. Deierhoi's question related to overall length of ischemia. We do not have an arbitrary cut-off. We do accept kidneys that come across the country and we put them on the pump. Frequently vascular resistance falls and most such kidneys recover their function promptly after revascularization.

It was asked if our aggressive use of ECD kidneys has had a negative impact on other transplant centers in our organ procurement organization. I do not think it has since many of the ECD kidneys were refused by them before they were accepted by us. Thus, we did not take away anything from them.